Microbiota and Covid-19. Which came first, the chicken or the egg?

Maria Antonietta Marcialis, MD, Flaminia Bardanzellu*, MD, Vassilios Fanos, Full Professor

Neonatal Intensive Care Unit, Department of Surgical Sciences, AOU and University of Cagliari. SS 554 km 4,500, 09042 Monserrato. Italy

* Corresponding Author: bardanzellu.flaminia@virgilio.it. 070/51093426. SS 554 km 4,500, 09042 Monserrato. Italy

Dear Editor,

We carefully read the article by Gu and colleagues,[1] reporting significant differences in the gut microbiota comparing patients affected by COVID-19, H1N1 and healthy controls.
Moreover, significant alterations in the fecal microbiome of COVID-19 patients during hospitalization were described.[2]
Gut microbial communities can interact with intestinal viruses promoting or contrasting their invasiveness, and being affected by them.[3]
Recently, the interlink between the gut microbiota, influenza virus and the severity of symptoms has been reported;[4] influenza pulmonary infection could significantly alter the intestinal microbiota profile through type I interferons (IFN-Is). Moreover, IFN-Is produced in the lungs can promote the depletion of obligate anaerobic bacteria and the enrichment in gut *Proteobacteria*, leading to "dysbiosis".[4]
Influenza viruses, including SARS-CoV-2, replicate in the respiratory tract but can reach and infect the gut, causing intestinal symptoms and interacting with local microbiota.[5]
Rarely, SARS-CoV-2 infection can cause hemorrhagic colitis; more frequently, it is associated with thickening and pneumatosis of the bowel with portal pneumatosis.[6] These effects can be favored by gut dysbiosis, but can also be promoted by impaired antibacterial defenses leading to infection, increased mucosal permeability, bacterial translocation.[7]
SARS-CoV-2 may interact with gut microbes in predisposed healthy controls and even in symptomatic COVID-19, and a different and specific microbiota composition can be detected. In the first group, a reduction in Lactobacilli and an increase in *Klebsiella spp.*, *Streptococcus spp*. and *Ruminococcus spp*. occurred. In hospitalized patients, a reduction in commensal bacteria and the increase in *Clostridia spp*., *Actinomyces spp*., and *Bacteroides spp*. was reported and, finally, not predisposed healthy controls were mainly characterized by commensal bacteria.[8]
These results are in agreement with Zuo et al. since COVID-19 reduces commensals and *Clostridia spp*. and seems to increase the disease severity;[2] a Chinese report confirmed a gut dysbiosis with decreased Lactobacilli and Bifidobacteria.[9] Modifications induced by SARS-CoV-2 seem different from those induced by H1N1 influenza, underlining as different viruses exert variable effects.[1]
Moreover, in a pre-print paper, fecal samples of affected patients showed metabolomics features suggesting amino acid pathways potentially linking gut microbiota to inflammation[8].
Dysbiosis and inflammation increase angiotensin-converting enzyme 2 intestinal expression, proportionally to SARS-CoV-2 fecal load,[2] potentiating its virulence.
Moreover, dysbiosis occurs in several comorbidities, including diabetes and obesity, and even in Kawasaki disease, characterized by the increase in *Streptococcus spp.* and a reduction in Lactobacilli.
A physiological gut microbiome (promoted by environmental factors including "healthy" diet, adequate vitamin D assumption, physical activity, lifestyle, reduced use of antibiotics and other drugs), in addition to genetics factors, comorbidities, age, sex, and geographical provenience, could have a determining role in promoting immune response and preventing an excessive anti-viral immune reaction. All these factors could explain the differences in the frequency and severity characterizing SARS-CoV-2 infection, since dysbiosis and inflammation (observed in elderly or immuno-compromised people and the metabolic syndrome) represent favoring factors.
In conclusion, we could hypothesize that specific interventions on gut microbiota, through prebiotics, probiotics, or involving nanotechnologies, will help in preventing or reducing COVID-19 symptoms even in predisposed patients affected by comorbidities.

Conflicts of interest

FB, VF and MAM have not conflicts of interest to declare.

References

1. Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, Guo F, Zhang X, Luo R, Huang C, Lu H, Zheng B, Zhang J, Yan R, Zhang H, Jiang H, Xu Q, Guo J, Gong Y, Tang L, Li L. Alterations of the Gut Microbiota in Patients with COVID-19 or H1N1 Influenza. Clin Infect Dis, **2020;** Jun 4:ciaa709. doi: 10.1093/cid/ciaa709. Epub ahead of print.

2. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung A, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology, **2020** ; 19: S0016-5085(20)34701-6. doi: 10.1053/j.gastro.2020.05.048.

3. Li N, Ma WT, Pang M, Fan QL, Hua JL. The Commensal Microbiota and Viral Infection: A Comprehensive Review. Front Immunol, **2019 ;** 10:1551. doi: 10.3389/fimmu.2019.01551.

4. Deriu E, Boxx GM, He X, Pan C, Benavidez SD, Cen L, Rozengurt N, Shi W, Cheng G. Influenza Virus Affects Intestinal Microbiota and Secondary Salmonella Infection in the Gut through Type I Interferons. PLoS Pathog, **2016** ; 12(5):e1005572. doi: 10.1371/journal.ppat.1005572.

5. Fanos V, Pintus MC, Pintus R, Marcialis MA. Lung microbiota in the acute respiratory disease: from coronavirus to metabolomics. J Pediatr Neonat Individual Med, **2020** ; 9(1):e090139. doi:10.7363/090139.

6. Carvalho A, Alqusairi R, Adams A, Paul M, Kothari N, Peters S, DeBenedet AT. SARS-CoV-2 Gastrointestinal Infection Causing Hemorrhagic Colitis: Implications for Detection and Transmission of COVID-19 Disease. Am J Gastroenterol, **2020** ; 115(6):942-946. doi: 10.14309/ajg.0000000000000667.

7. Di Grezia M, Fransvea P, Santullo F, Tirelli F, Fico V, Mirco P, Cozza V, La Greca A, Sganga G. Intra-abdominal hypertension as a trigger of "gut failure" in SARS-CoV-2 infection: Effect of open abdomen (OA) and negative pressure therapy (NPT) on respiratory and gastrointestinal (GI) function. Med Hypotheses, **2020** ; 144:109954. doi: 10.1016/j.mehy.2020.109954. Epub ahead of print.

8. Gou W, Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. doi: https://doi.org/10.1101/2020.04.22.20076091

9. Xu K, Cai H, Shen Y, Ni Q, Chen Y, Hu S, Li J, Wang H, Yu L, Huang H, Qiu Y, Wei G, Fang Q, Zhou J, Sheng J, Liang T, Li L. [Management of corona virus disease-19 (COVID-19): the Zhejiang experience]. Zhejiang Da Xue Xue Bao Yi Xue Ban, **2020** ; 49(1):0. Chinese.